Journal of Clinical Anesthesia xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Methadone versus morphine for postoperative pain in patients undergoing surgery for gynecological cancer: A randomized controlled clinical trial☆

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ARTICLE INFO

Keywords:
Postoperative pain
Morphine
Methadone
Opioids
Gynecological cancer

ABSTRACT

Study objective: The aim of this study was to compare methadone and morphine for the management of post-operative.
Design: Open, controlled study.
Setting: Postoperative recovering area, ward.
Patients: Sixty-four patients, ASA I-III, undergoing gynecological surgery for cancer.
Interventions: Morphine or methadone 0.15 mg/kg given preoperatively. After operation an intravenous morphine or intravenous methadone infusion at doses of 12 mg/day was started.
Measurements: Pain intensity and opioid consumption.
Main results: Methadone infusion provided a better analgesia in comparison with morphine infusion on the second day. Opioid consumption was significantly lower in the methadone group. No episodes of relevant desaturation or signs of respiratory depression were recorded.
Conclusion: A preoperative bolus of methadone, followed by a continuous infusion of low doses post-operatively, provided a better analgesia, without adding risk of adverse effects, in comparison with morphine.

1. Introduction

Adequate postoperative pain control is an important part of perioperative medicine. Inappropriate perioperative pain management has numerous physiologic complications and is responsible of unnecessary suffering [1]. Regretfully, many patients remain undertreated. It has been reported that > 40% of patients report inadequate pain relief or pain of moderate intensity or greater in the postoperative period, despite treatment [2,3]. Of concern, unrelieved postoperative pain increases risk of developing chronic post surgical pain [1].

Intravenous patient-controlled analgesia (PCA) has become the mainstay for providing postoperative pain relief over the past years [4–6]. However, PCA may have some limitations. While PCA may reduce nursing time, the cost of pumps, disposables, and adverse events should be considered in balancing the overall cost-effectiveness of PCA. [7]. For many years a long-available effective drug, such as methadone, has been underutilized. Despite methadone being a cost-effective analgesic for acute, chronic, neuropathic, and cancer pain, and can be administered via oral and parenteral routes [8], its use in the operating room and postoperatively is a neglected issue [7]. Only few old studies have assessed methadone for postoperative pain [9–12]. These studies were performed in a mixed population undergoing different surgeries and were principally based on a pre-operative administration of a methadone bolus.

The primary aim of this study trial was to compare the effects of methadone on pain scores with those of morphine for postoperative pain in patients undergoing a standard operation, like hysterosalpingectomy for gynecological cancer. In addition, the analgesic requirements and possible adverse effects induced by opioids were determined.

☆ This paper was written according to CONSORT recommendations (Fig. 1). The study was not registered, as it is not requested in our country. It was prepared before 2015, when most journals introduced the need to register trials. Moreover, there were no changes of the original protocol and all data of this trial have been included and were not replied in other studies, as redundant publication.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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https://doi.org/10.1016/j.jclinane.2019.109627
Received 6 May 2019; Received in revised form 12 September 2019; Accepted 20 September 2019
0952-8180/

2. Methods

This was a randomized, active-controlled, study. The study protocol and statement of informed consent were approved by the institutional review board Ethical approval for this study (Ethical Committee N° 6/2013) was provided by the Ethical Committee of the University of Palermo. All patients provided written informed consent. Patients were recruited in a period of two years.

Patients scheduled for open hystero-salpingectomy for gynecological cancer under general anesthesia were enrolled. Non-pregnant female patients were eligible for inclusion if they were at least 18 years old and had an American Society of Anesthesiologists physical status I to III. Patients were excluded if they were receiving opioids for chronic pain or for any other reason, had documented sleep apnea, alcohol or drug abuse, oxygen saturation of < 92%, had any medical condition that would interfere with pain assessment. The use of any drug that would affect postoperative pain levels, such as gabapentinoids, steroids, or anti-inflammatory drugs was not allowed intraoperatively or postoperatively. Patients with a chronic pain condition necessitating treatment with these agents were also excluded from the study. Patients had to be withdrawn from the study if the oxygen saturation could not be maintained at ≥92% with supplemental oxygen (3 L/min), if the respiratory rate could not be maintained at 8 breaths/min or greater, or if excessive sedation occurred.

2.1. Procedures

Patients scheduled for the first operation during the day (performed at 8 AM), were randomized by a computerized system to receive morphine (group 1) or methadone (group 2). A total of 64 participants were randomized chronologically in a 1:1 ratio according to the random coding table and were given the corresponding medication.

Patients were premedicated with midazolam 0.1 mg/kg, plus morphine or methadone 0.15 mg/kg, intravenously. During surgery, intravenous fentanyl was allowed as needed for analgesia. Nasogastric tube was not inserted. Following surgery, boluses of the study drugs in doses of 3 mg were given to keep the patient comfortable in the post-anesthesia care unit (PACU) if their pain intensity was ≥4/10. These doses were computed in opioid consumption calculation on the operation day. Pain intensity was based on an 11-point numerical rating scale (NRS), where 0 = no pain and 10 = worst possible pain. Metoclopramide 5 mg and clonidine 75 μg were given in case of vomiting and shivering, respectively, during PACU stay.

At discharge from the PACU, an intravenous morphine or methadone infusion was given, at doses of 12 mg/day. Paracetamol was given first at request of patients. Extra-doses of morphine or methadone in doses of 3 mg were given as breakthrough medication. Patients were educated about asking for opioid analgesia when pain was considered no longer acceptable. The use of metoclopramide was permitted for controlling nausea and vomiting.

Comorbidities and some parameters such as, pain intensity (numerical scale 0–10), the level of nausea, drowsiness, and itching (from 0 to 3), episodes of desaturation (< 92%) were recorded since the patient was transferred to the surgical ward at 12 AM, and 2, 4, 6, 8, and 10 PM on the operation day, labelled as T1, T2, T3, T4, T5, and T6, respectively. On the second day, these parameters were measured at 6 and 10 AM, and 2, 6, and 10 PM, labelled as T7, T8, T9, T10, and T11, respectively. Opioid consumption was recorded in the PACU and in the surgical ward on the operation day, and on the second day.

The primary efficacy end point was the pain intensity at the different time intervals on operation day and on the second day. Secondary end points included the pain intensity differences (PID), and the time-weighted summed pain intensity difference over 48 h (SPID48), as well as the opioid consumption, as extra-doses of the study drugs given at patients' request.

2.2. Statistical analysis

To achieve the primary end point, a sample size of 20 patients per treatment group yields a statistical power of 80% with a Type 1 error of 0.05, allowing the detection of a difference of 0.5 in mean pain intensity score (with a standard deviation of 0.5). The within-group standard deviation is assumed to be 3, with a percentage of missing data of 20%. The sample size was inflated by 40% to account for missing data, attrition, and protocol violations.

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Continuous data are expressed as mean ± SD, unless otherwise specified. Frequency analysis was performed using the Pearson's chi-square test and Fisher exact test, as needed. The univariate analysis of variance (ANOVA) was performed to evaluate mean differences (age, weight, and opioid consumption) between patient groups. Whereas some variables were not normally distributed, we have used non-parametric tests and in particular the related-samples Friedman's two-way analysis of variance by ranks test (for intragroup comparison) and the independent-samples Mann-Whitney *U* Test for intergroup comparison. Data were analyzed by IBM SPSS Software 22 version (IBM Corp., Armonk, NY, USA). All P-values were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

Sixty-four patients met the inclusion criteria. Four patients had incomplete data. Thus, 60 patients were examined (32 and 28 patients in group 1 and 2, respectively). The flow diagram, according to CONSORT guidelines is reported in Fig. 1. The mean age was 56.3 years (SD 9.6), and the mean weight was 64.6 kg (SD 9.4). No differences between the two groups were found ($P = 0.799$ and 0.909, respectively). Fifty, nine, and one patients were ASA II, III and I, respectively, with no differences between the groups (Fisher's exact test $P = 0.209$). Also the distribution of comorbidities in morphine vs methadone group was similar for hypertension (12 vs 14 patients respectively, Fisher's exact test $P = 0.435$), diabetes (2 vs 5 patients respectively, Fisher's exact test $P = 0.235$), chronic respiratory disease (2 vs 1 patients respectively, Fisher's exact test $P = 1.0$), and obesity (6 vs 3 patients respectively, Fisher's exact test $P = 0.482$). No episodes of relevant desaturation were recorded and no patient presented signs of respiratory depression.

The changes of parameters recorded at the different time intervals on the operation day and on the second day are shown in Tables 1 and 2. Pain intensity progressively changed in both groups. Methadone infusion provided a better analgesia in comparison with morphine infusion on the second day. PID at the various intervals and SPID48 are reported in Tables 3 and 4, respectively. The difference was significant for PID at the last measurements on the second day. Lower values of SPID48 were found in the methadone group, although the difference was not significant different between the two groups.

Intravenous paracetamol was used in 20 and 14 patients in morphine and methadone groups, respectively (Fisher's exact test $P = 0.435$). Opioid consumption was significantly lower in the methadone group (Table 5).

4. Discussion

The findings of this study suggest that a preoperative dose of methadone, followed by a continuous infusion of low doses of methadone, provided better postoperative analgesia in patients undergoing in comparison with morphine in patients undergoing gynecological procedures. Moreover, analgesic consumption including paracetamol and study drugs was significantly lower in patients receiving methadone. This analgesic effect was not associated with more adverse effects among those commonly induced by opioids.

These findings are explained by several pharmacologic and clinical

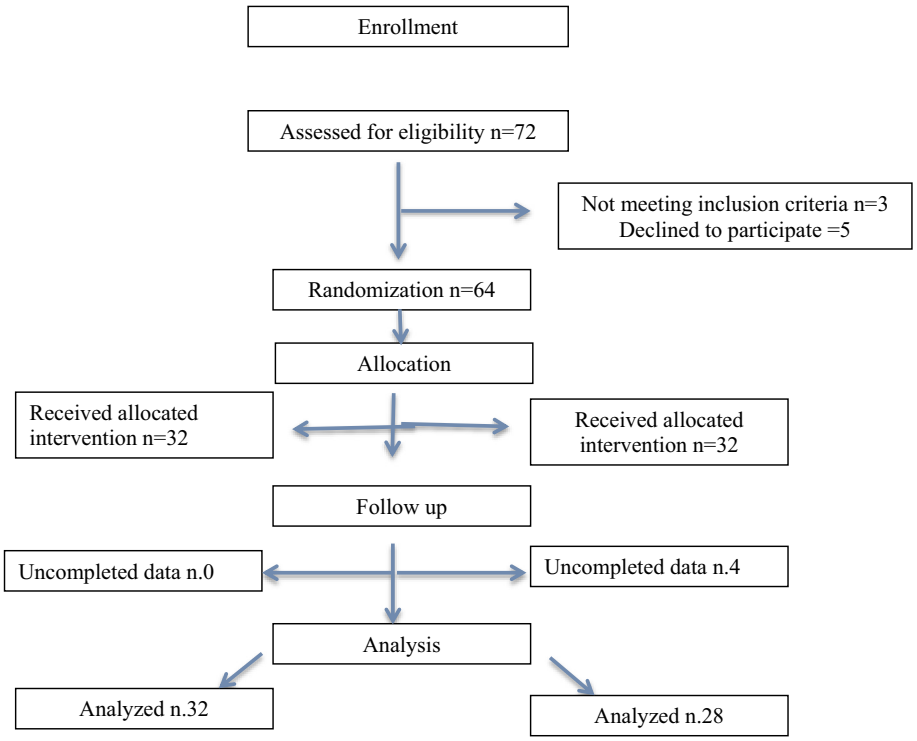

Fig. 1. CONSORT flow diagram.

Table 1
Changes of parameters recorded on the operative day (T1, T2, T3, T4, T5, T6 correspond to 12 AM, and 2, 4, 6, 8, and 10 PM, respectively.)

		T1	T2	T3	T4	T5	T6	P intergroup[a]
Pain intensity	Morphine	4.5 (2.1)	3.5[§] (2.4)	2.3* (1.9)	1.6* (2.1)	0.9* (1.4)	0.6* (1.2)	T1 P = 0.018
	Methadone	3.0 (2.2)	2.1^ (2.3)	1.2* (1.4)	0.8* (1.3)	0.5* (1.2)	0.3* (0.9)	T2 P = 0.013
								T3 P = 0.009
Nausea	Morphine	0.4 (0.9)	0.3 (0.7)	0.2 (0.5)	0.1 (0.3)	0.2 (0.7)	0.2 (0.4)	T1 P = 0.021
	Methadone	0.04 (0.2)	0.1 (0.3)	0.1 (0.3)	0.3 (0.7)	0.1 (0.4)	0.2 (0.7)	
Vomiting	Morphine	0.03 (0.2)	0.06 (0.2)	0.09 (0.3)	0.0 (0.0)	0.06 (0.2)	0.06 (0.2)	NS
	Methadone	0.04 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.04 (0.2)	0.07 (0.2)	NS
Drowsiness	Morphine	1.5 (0.6)	1.5 (0.8)	1.2 (0.8)	1.1^ (0.6)	1.0[§] (0.7)	0.5* (0.5)	NS
	Methadone	1.3 (0.6)	1.3 (0.9)	0.9^ (0.7)	0.8^ (0.7)	0.7[§] (0.8)	0.4* (0.6)	NS
Itching	Morphine	0.03 (0.2)	0.03 (0.2)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NS
	Methadone	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NS

^ $P < 0.05$ vs T0.
* $P < 0.0005$ vs T0.
§ $P < 0.005$ vs T1, related-samples Friedman's two-way analysis of variance by ranks.
[a] Independent-samples Mann-Whitney *U* test.

studies, although few trials assessed the value of methadone as a postoperative analgesic drug. It still remains a misunderstood drug [7], possibly due to some misconception about its use in the perioperative setting, due to its onset, duration, and metabolism. The onset of methadone is relatively fast, comparable to fentanyl, as central nervous system effect site methadone concentrations rapidly equilibrate with plasma concentrations [13], corresponding to the time course of miosis. Of interest, a lag time exists for the central nervous system compartment penetration and the onset time of morphine [14]. Thus methadone can be considered as a rapid-onset drug, with an onset time similar to that of fentanyl.

It has been reported that the duration of methadone analgesia is shorter than its elimination half-life. However, this observation is also true for other opioids as well other drugs [15,16]. Targeting doses and concentrations above the minimal analgesic concentration but below the threshold for respiratory depression, should provide a lasting analgesia and minimal central adverse effects. Of interest, a calibrated continuous infusion with low doses may overcome the problem, as it occurred in this study. Although methadone has a highly variable clearance and a large potential for drug interactions [17], these interferences are often subclinical [7,18].

Pioneer investigations on methadone in the perioperative period were reported about 30 years ago [9–12]. An intravenous bolus of 20 mg of methadone, after induction of anesthesia, determined a complete analgesia in approximately one-third of patients, and no analgesic requests during the 72 hour postoperative observation period were reported. Only one third of patients requested some postoperative opioid drugs, and the mean time to first opioid analgesic request was 20 h. These outcomes were achieved without reporting relevant adverse effects.

After many years, data regarding the use of methadone in the perioperative setting still remain poor, particularly in abdominal cancer surgery. In patients undergoing hip arthroplasty a continuous infusion of 24 mg/day of methadone with PCA boluses of 1 mg, determined a lower opioid consumption and less pain in comparison with morphine, while adverse effects were similar [19]. In a randomized trial, patients

Table 2
Changes of parameters recorded on the first postoperative day (T7, T8, T9, T10, and T11 correspond to 6 and 10 AM, and 2, 6, and 10 PM, respectively).

		T7	T8	T9	T10	T11	P intergroup[a]
Pain intensity	Morphine	2.3 (1.8)	2.0 (1.6)	1.0[§] (1.1)	1.1[§] (1.4)	0.5[*] (0.8)	T7 P < 0.0005
	Methadone	0.6 (1.0)	0.6 (1.6)	0.3 (0.7)	0.07 (0.4)	0.0 (0.0)	T8 P < 0.0005
							T9 P = 0.003
							T10 P < 0.0005
							T11 P = 0.003
Nausea	Morphine	0.4 (0.7)	0.2 (0.4)	0.03 (0.2)	0.09 (0.4)	0.03 (0.2)	NS
	Methadone	0.5 (0.9)	0.3 (0.5)	0.1 (0.6)	0.07 (0.3)	0.1 (0.4)	
Vomiting	Morphine	0.2 (0.4)	0.0 (0.0)	0.03 (0.2)	0.03 (0.2)	0.0 (0.0)	NS
	Methadone	0.1 (0.4)	0.1 (0.3)	0.07 (0.3)	0.04 (0.2)	0.04 (0.2)	NS
Drowsiness	Morphine	0.7 (0.5)	0.7 (0.7)	0.4[^] (0.6)	0.2[#] (0.5)	0.1[#] (0.4)	NS
	Methadone	0.6 (0.6)	0.4 (0.5)	0.2[^] (0.4)	0.2[^] (0.4)	0.1[^] (0.3)	NS
Itching	Morphine	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NS
	Methadone	0.0 (0.0)	0.04 (0.2)	0.04 (0.2)	0.0 (0.0)	0.0 (0.0)	NS

[#] P < 0.001 vs T0.
[*] P < 0.0005 vs T0.
[§] P < 0.005 vs T0.
[^] P < 0.05 vs T0; related-samples Friedman's two-way analysis of variance by ranks.
[a] Independent-samples Mann-Whitney *U* test.

Table 3
Pain intensity difference at the selected intervals.

		Operation day						Second day				
		T1–T2	T2–T3	T3–T4	T4–T5	T5–T6	T1–T6	T7–T8	T8–T9	T9–T10	T10–T11	T7–T11
Morphine	Mean (SD)	1.0 (2.4)	1.2 (2.1)	0.7 (1.7)	0.72 (1.6)	0.3 (1.1)	3.84 (2.1)	0.3 (2.0)	0.9 (1.4)	0.0 (1.6)	0.6 (1.0)	1.8 (1.7)
Methadone	Mean (SD)	0.9 (2.5)	0.9 (1.9)	0.4 (0.9)	0.3 (1.2)	0.2 (0.5)	2.7 (2.4)	0.1 (1.8)	0.3 (1.5)	0.3 (0.8)	0.1 (0.4)	0.6 (1.0)
P intergroup[a]		0.826	0.487	0.152	0.210	0.758	0.057	0.767	0.007	0.835	0.006	0.005

[a] Independent-samples Mann-Whitney *U* test.

Table 4
SPID 48 in morphine and methadone groups.

	N	Mean	Std. deviation	Std. error	95% confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
Morphine	32	29.2188	20.82451	3.68129	21.7107	36.7268	−20.00	62.00
Methadone	28	23.5714	21.58262	4.07873	15.2026	31.9403	−23.00	64.00
Total	60	26.5833	21.19185	2.73586	21.1089	32.0578	−23.00	64.00

P = 0.378, independent-samples Mann-Whitney *U* test.

Table 5
Opioid consumption in the two groups; univariate analysis of variance (ANOVA test).

		N	Mean	DS	P
Operation day	Morphine mg	32	6,09	4,067	0.002
	Methadone mg	28	3,11	2,998	
Second day	Morphine mg	32	2,25	2,851	< 0.0005
	Methadone mg	28	0,11	0,567	

undergoing vertebral surgery, received an initial loading dose of 0.75 μg/kg sufentanil before surgical incision and a sufentanil infusion of 0.25 μg/kg/h or methadone infusion, 0.2 mg/kg, after intubation. In comparison with sufentanil, methadone significantly reduced the opioid consumption and pain scores in the postoperative period [20]. In a similar surgical population, preoperative methadone 0.2 mg/kg conferred a longer analgesia and less opioid consumption in comparison with hydromorphone 2 mg, given at the end of surgery [21,22], although the doses chosen (about 15 mg and 2 mg, for methadone and hydromorphone, respectively) should not be considered to be equivalents [23]. According to these data, an initial priming with methadone provided a prolonged and effective analgesia. These effects were attributed to the slow rate of methadone elimination, and a *N*-methyl-D-aspartate receptor antagonism [7].

In a gynecological cancer population similar to that examined in this study, methadone and morphine in doses of 20 mg were given after induction of anesthesia. Patients who were administered methadone required less methadone than morphine in the recovery room and on the wards, and reported lower pain intensity scores [24]. Similarly, in women undergoing abdominal hysterectomy, methadone or morphine, 0.25 mg/kg were given preoperatively with further increments in the recovery room for analgesia. Patients in the methadone group had lower pain scores in the subsequent 48 h and had a less opioid consumption [25]. Taken together, these data are consistent with a sustained therapeutic analgesic effect in the postoperative period. In the present study, a preoperative bolus of methadone and a postoperative infusion of low doses provided superior analgesia over morphine, suggesting that methadone is an effective and safe drug for postoperative pain. Of interest, intravenous infusion of methadone has been used for cancer pain management in opioid-tolerant patients, successfully [8].

There are some limitations of this study. Only women and a typical gynecologic surgery were chosen. Gynecological procedures were chosen as they are standard operations in terms of duration and potential capacity to produce postoperative pain.

In conclusion, a preoperative bolus of methadone, followed postoperatively by a continuous infusion of low doses provided a potent

analgesia, without adding risk of adverse effects, in comparison with morphine. More information is needed about the effectiveness and safety in outpatients, those who are opioid tolerant, and the cost-effectiveness of methadone in comparison with other opioids or conventional PCA in the different surgeries. Nevertheless, the findings of this study suggest that it is opportune to reappraise the use of methadone in the perioperative period.

Declaration of competing interest

None.

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